REMARKS

Applicants are amending the specification herein, at the request of the Office, to update the continuity data on page 1 and to acknowledge trademarks used in the description. Applicants request entry of these amendments. No new matter is added.

Claims 1-4 are rejected under 35 U.S.C. §112, second paragraph, as indefinite for recitation of the term "vaccine" because the claims do not specifically recite the disease or infection the vaccine is to protect against. Applicants have amended claim 1 herein to recite "against human cytomegalovirus." Applicants refer the Office to the entire specification as originally filed and specifically at paragraphs 3, 9, 24 and 52 for support for this amendment and request that the rejection of the claims on grounds of indefiniteness be withdrawn. Applicants also have added new claims 5-8, which are directed to an "immunogenic composition for modifying the immune response of a mammal to human cytomegalvirus." These claims are supported by the original specification, specifically at paragraphs 26, 30, 46, 50 and 51, and Example 11.

Claims 1-4 are rejected under 35 U.S.C. §112, first paragraph, as not enabled. In particular, the Office asserts that no examples in the specification disclose or teach a vaccine comprising the peptides recited in the claim and the specification does not set forth any guidance as to which sequence provides vaccine protection. The Office concludes that, because the art is unpredictable (citing a seven-year-old paper

and other art), and the specification assertedly lacks guidance as to how to use the claimed vaccine to protect against HCMV infection, undue experimentation would be required to practice the invention.

Applicants respectfully submit that this rejection is not proper and is based on misapprehensions concerning the invention, the disclosures of the specification and the cited art.

The Office describes in superficial terms, the contents of the present application's teachings by listing the titles of Examples, reducing the content of the application to a few bullet points. Applicants respectfully submit that this is an unfair characterization of the contents of the specification. The disclosures of the specification describe not only how the peptides were discovered, but how they were tested for parameters well-known in the art to correlate with usefulness as a vaccine and how the peptides can be used.

In general terms, the application as filed discusses the method of eliciting virus-specific CTL by immunizing with a vaccine peptide representing a minimal cytotoxic epitope defined for a viral antigen in the context of a particular MHC restriction element. See pages 3-4. This is discussed as part of the prior art. The embodiment of the invention claimed here improves upon the prior vaccine peptide methods by providing vaccines comprising the recited sequences, which are novel as acknowledged by the Office (Office Action, item 8, page 5). The application goes into great detail explaining why the peptides discussed in the application are more immunogenic than the known

CTL epitopes which are vaccine peptides that "elicit[] CTL that control or clear viral infections." See page 5, paragraph 13.

What is routine in the art is preferably omitted from a patent application. Furthermore, the Office has the burden of advancing adequate reasons why the person of ordinary skill in the art could not perform the claimed invention without undue experimentation. Here, the claims are limited to a vaccine which comprises a peptide of a recited group. Since the sequences have been provided, the person of skill would be able to synthesize or otherwise obtain the peptides. Methods of formulating vaccines to provide the sequences to an individual are well-known in the art, including methods for formulation and preparation discussed in the application at pages 20-21. This discussion teaches methods of administering the peptides alone, with adjuvant, lipidated, as a cellular vaccine, with T helper peptides such as PADRE, as a fusion with a CD4 peptide epitope, with or without linkers, and so on. Any skilled person would be able to formulate numerous vaccine compositions comprising the recited peptides, without any experimentation at all, even without such guidance. With the guidance provided, however, the skilled person would be able to perform any routine adaptations to increase vaccine effectiveness as discussed in the specification, for example by fusing the peptide with a T-helper epitope or by using a DNA adjuvant, or other methods as discussed.

The only other issue which seems to remain in the reasoning of the Office is the unsubstantiated doubt that the vaccine peptides claimed, when formulated according to known methods using the guidance of the specification, would actually <u>function</u>

as a vaccine, since the application and the prior art clearly teaches how to make the vaccine peptides, how to make them into a vaccine composition, and how to administer the composition (use them), which is all that is required to meet the standards of 35 U.S.C. §112, first paragraph (enablement). See M.P.E.P. §§2164.01(b), (c), which refer to how to make the invention and how to use it. It is not necessary to specify a method of use if one skilled in the art, based on knowledge regarding compounds having similar activities, would be able to discern the method. M.P.E.P. §§2164.01(c).

In attempting to meet its burden to provide a reasonable basis to question the presumptively accurate assertions in the specification that the peptides claimed here serve as vaccines, the Office states only that no example sets forth a vaccine that was administered and that the art generally is unpredictable. The specification does, however, show that the claimed peptides have improved vaccine characteristics over native sequences that are known to be involved in cellular immunity for HCMV, as discussed in the originally filed application. Applicants also refer the Office to U.S. Patent No. 6,726,910, commonly assigned with the present application, and its parent applications.

This patent discloses and claims vaccine peptides which are native CTL epitopes of HCMV and which were shown, in a well-accepted mouse model to elicit cellular responses to HCMV. Furthermore, the native CTL epitope, SEQ ID NO: 1, against which the claimed peptides are compared, is known to play an important role in CMV immunity and to be a major indicator of CMV immunity in humans.

An applicant is required to provide one method for making and using the claimed invention that bears a reasonable correlation to the scope of the claim. See M.P.E.P. § 2164.01(b). This, applicants have done, as discussed above. No skilled person would have difficulty in making a vaccine or immunogenic composition as claimed given the knowledge in the art and the copious guidance in the specification. In essence, the Office asserts a lack of enablement not because there is doubt that a skilled person could make the claimed invention or use the claimed invention, but rather that the invention would not work, an argument related to credible utility rather than enablement. To satisfy the requirement for credible utility, an Applicant must provide a credible assertion of specific and substantial utility. See M.P.E.P. § 2107(II). If the Office doubts the credibility of the utility of an invention, the Office must establish that the skilled person would not consider the utility as asserted to be credible. This showing must contain a clear explanation of the reasoning for the conclusion that the utility is not credible, support for factual findings relied upon in reaching this conclusion, and an evaluation of all relevant evidence, including utilities taught in the closest prior art.

The Office's rejection, however, is based on principles of law relating to enablement, and hence the contents of the specification. For example, the Office Action states that none of the examples set forth or teach a vaccine that was administered to a subject. This disclosure (or perceived lack of it) does not affect whether a skilled person can administer the vaccines taught in the specification to a subject. As discussed

above, the specification provides a great deal of discussion on how to formulate vaccines from peptides. The skilled person would have had no difficulty administering these vaccines to a subject, for example by intranasal or intramuscular administration, which was well known in the art. It is not clear from the Office Action what experimentations would be required by the skilled person to make the vaccine or to use the vaccine.

The Office's contentions that the vaccines (and immunogenic compositions) which are claimed as compositions of matters do not function, are based for the most part on statements that, prior to this application's filing date, peptides had not been proven to provide vaccine protection in the art cited. Applicants submit that this is insufficient reason to doubt the utility or function of these compositions in light of what is known about the usefulness of these epitope peptides in influencing CMV immunity.

The peptide of SEQ ID NO: 1 is well-known to be the major epitope responsible for CMV recognition in HLA A*0201 humans. See Gratama and Cornelissen, *Clin. Immunol.* 106:29-35, 2003, Table 1 and cited references; see also specification at paragraph 9. For example, it is clear that hematopoietic stem cell transplant recipients (HLA A*0201) who do not recover CD8+ T cells specific for SEQ ID NO:1 were more likely to develop CMV disease and that protection against progressive CMV infection and CMV disease is confirmed by these specific T cells. See, for example, Gratama et al., *Blood* 98(5):1358-1364, 2001 at page 1362, right column, Cwynarski et al., *Blood* 97(5):1232-1240,

2001, abstract and page 1239, and the art cited in the accompanying Information Disclosure Statement.

In addition, these T cells, identified by staining with HLA-peptide tetramer reagents, have transferred functional CMV immunity to patients who received them. See Moss et al., abstract; Einsele et al., Blood 99(11): 3916-3922, 2003. The peptide of SEQ ID NO: 1 therefore is recognized in the art as a human CTL epitope which is effective to produce immunity in humans. The Office's assertion regarding the asserted failure in the prior art to prove "long-term immunity in seronegative individuals" is not relevant here because applicants are not required to prove such aspects of vaccine use were available in the prior art in order to show that the claimed compositions are enabled, useful or even are useful as a vaccine. Producing long-term immunity in seronegative individuals is only one potential use of a vaccine composition. Vaccines also are given to infected persons to boost the immune response. See specification at paragraph 25, for example. It is clear from the totality of the art that SEQ ID NO:1 is useful in producing modifications in the immunity to CMV in humans, and moreover is beneficial in terms of reducing CMV disease. Since the claimed peptides were compared to SEQ ID NO: 1 using assays which examine the same characteristics of SEQ ID NO:1 well-recognized to make it useful in humans, no skilled person would doubt the function of the claimed peptides, or have any difficulty in making or using them as claimed.

The peptides here claimed were compared to their corresponding native CTL epitopes (SEQ ID NO: 1 of the present

application and SEQ ID NO: 1 of U.S. Patent No. 6,726,910) and found to be superior using standard tests. Given this context and the general knowledge in the art with respect to the well-acknowledged assays performed for and discussed in the present application, which show a high level of activity for the claimed peptides in terms of sensitivity of recognition and breath of recognition (see Example 11), Applicants submit that the Office has not provided a reasonable basis to doubt that the vaccine peptides are useful as vaccines and therefore are enabled.

With respect to the particular art cited by the Office, the Diamond et al. reference cited by the Office is dated 1997 and is of no relevance with respect to the quality of enabling disclosure in the present application. It is cited only for its own asserted failure to "achieve" vaccine protection in 1997 because it generally refers to peptides as "candidates." Applicants refer the Office to the present specification and to U.S. Patent No. 6,727,910 and its parent applications, discussed above. The Zaia et al. reference likewise is cited only because it assertedly fails to provide vaccine protection. This review article summarizes research and theory concerning CMV prevention and treatment up to the year 2000 and is dated January, 2000. Its contents have no significance in determining whether the present specification enables the skilled person to make and use the claimed vaccine peptides, which are not even mentioned in Zaia et al. Given the known characteristics of SEQ ID NO: 1 with respect to human CMV immunity and the comparative data shown here, the present application status that the peptides have

utility. There is no reason why the skilled person would doubt this statement.

BenMohamed et al. is cited for "appear[ing] to suggest" that Th epitopes should or must be included in an epitope-based design. The reference discusses different strategies and forms part of the state of the art near the priority date of this application, but again, its disclosures are in no way relevant to the sufficiency of the support to enable the rejected claims. Furthermore, the specification does teach that T help may be included in the vaccines of the invention and provides guidance as to how this may be achieved. Applicants refer the Office to the specification at paragraphs 52-54, which discuss alternative vaccines that include separate or fused T lymphocyte help and the surrounding information which discusses other alternative to make useful vaccines using the peptides.

Applicants respectfully submit that, at most, these references either demonstrate a need in the art which the present invention fulfills or merely provide information already taught in the specification and generally in the art concerning how to make and formulate a vaccine. The totality of the art demonstrates that SEQ ID NO:1, and therefore the claimed compositions which have enhanced immunogenicity in comparison, is useful at moderating CMV immunity and therefore as a vaccine. The Office has not provided any meaningful explanation as to why the skilled artisan would not be able to make a vaccine comprising the recited peptides using knowledge in the art and guidance in the specification and to use the vaccine by administration to a subject. Moreover, there is no reason to

doubt that the vaccine would not modify CMV immunity. Applicants submit that they are not required to prove that all seronegative persons receiving the vaccine would obtain long-term immunity. This is only one potential use of a vaccine.

The specification as filed provides more than sufficient guidance to demonstrate that the claimed peptides possess the characteristics known to result in modification of the immune system to increase responsiveness to important HCMV antigens known to be part of successful immunity in humans. Applicants therefore request that the rejection of the claims be withdrawn and the application proceed to issuance at this time.

Respectfully submitted,

By _____

Martha Cassidy
Attorney for Applicants
Registration No. 44,066
ROTHWELL, FIGG, ERNST & MANBECK, P.C.
Suite 800, 1425 K Street, N.W.
Washington, D.C. 20005
Telephone: (202) 783-6040

1954-433.amd2.wpd